Current status of Ovarian Hyperstimulation Syndrome research

Marta Badia Garcia
Biomedical Science degree · Treball fi de grau 2014-2015

Universitat Autònoma de Barcelona

Introduction

The **Ovarian Hyperstimulation Syndrome (OHSS)** was first described in 1943 by Rydberg *et al.* as a loss of control over the intended therapeutic stimulation of the ovaries. In 1951, the first fatal case of OHSS was reported and it immediately became a potential complication associated with assisted reproductive techniques (ART), particularly with controlled ovarian stimulation (COS). Nowadays, it is considered the major risk related to ART just behind multiple pregnancies (1). In 2012, OHSS was reported in 0.6% European women undergoing a cycle of ovarian stimulation.

The central factor in triggering OHSS is an **hCG exposure**, either endogenous or exogenous, and it is because of the different source of this hormone that becomes its principal classification (*Table 1*):

- **Iatrogenic OHSS** or associated with COS
- **Sporadic OHSS** or spontaneous in pregnancy

Table 1. OHSS classification

Type	Iatrogenic OHSS	Sporadic OHSS
hCG source	Exogenous	Endogenous
Debut	~3-7 days post-hCG administration in COS	~8-14th pregnancy week
Incidence	Mild: 20-33% COS Moderate: 3-6% COS Severe: 0'1-2% COS	Indeterminable (literature based on case reports)

In both cases, it consists in a self-limiting syndrome in which the symptoms decline 10-14 days after its debut. The first symptoms are abdominal discomfort and distention, nausea, vomit and/or diarrhoea. At that point, vascular permeability increases resulting in protein-rich fluid from the intravascular space to mesothelium superficies, being this characteristic the cardinal feature of OHSS. The symptoms which follow this event depend on the severity of the syndrome (*Figure 1*)(2).

Even though the main mediators of the syndrome are known, today many aspects of **OHSS aetiology remain unclear.** It has not been elucidated why only a group of patients develop this life-threatening syndrome.

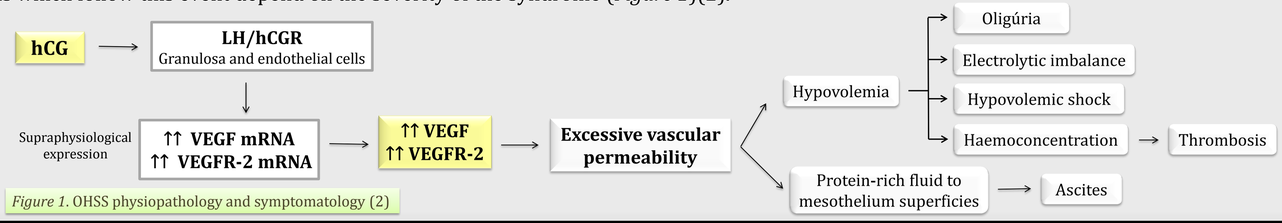

Figure 1. OHSS physiopathology and symptomatology (2)

Current research of OHSS

- **Basic research:**
  - Syndrome aetiology
- **Clinical research:**
  - Prevention/Treatment strategies
  - Risk factors analysis
  - Short/long-term consequences analysis

Aims and methodology

The aims of this review are :

- To show the most relevant results of OHSS basic research. Issues related to individual susceptibility and genetic aetiology.
- To show the focus of OHSS recent clinical research.

Scientific literature has been searched on PubMed database prioritizing those reviews and meta-analysis published in the last 5-10 years using keywords such as 'OHSS' ([AND]) 'pathology', 'VEGF', 'genetics', 'treatment', 'cancer' etc.

Relevant results in BASIC RESEARCH

Individual susceptibility in high-risk patients

High-risk OHSS patient's determination previous to ovarian stimulation has been the most useful tool in the prevention of the syndrome at the clinical practice .

Risk factors → Young women (30-35y), low IMC, PCOS, ↑ antral follicles nº, ↑ oestradiol...

Nevertheless, the long-standing problem has been that, in some cases:

- Patients considered at high-risk for OHSS have not developed the syndrome
- Patients not considered at high-risk for OHSS have developed the syndrome

→ **INDIVIDUAL SUSCEPTIBILITY**

Recent studies have concluded that the responsible for this intricacy are the **soluble VEGF receptors (sVEGFR)** (*Figure 2*). Those receptors bind to VEGF and avoid its function by preventing the interaction with its receptor VEGFR-2 (3). Thus, the vascular permeability remains stable.

High-risk patients → Who develop OHSS → **↓sVEGFR and ↑VEGF**
High-risk patients → Who don't develop OHSS → **↑sVEGFR and ↓VEGF**

sVEGFR analysis for OHSS prevention
sVEGFR use in OHSS treatment

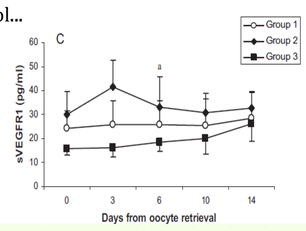

Figure 2. Normal (Group1) and high-risk women who don't develop (Group2) and who develop OHSS (Group3). sVEGFR1 plasma concentration is significantly lower in group3.

Genetic aetiology of OHSS

The multiple reported cases of sporadic OHSS in members of the same family sparked the interest in the research of a possible genetic aetiology of the syndrome. In 2003, *Vasseur et al.* and *Smits et al.* confirmed this hypothesis by detecting **activating polymorphisms in FSHR gene**. Over the years, many investigators have identified other polymorphisms sequencing the same gene and, in all cases, it has been demonstrated that FSHR mutations **broaden the specificity of this receptor** (*Table 2*). Then, it can be activated either by FSH or hCG. In some cases it can also be activated by TSH as a consequence of the homology between all these hormones (*Figure 3*)(4,5).

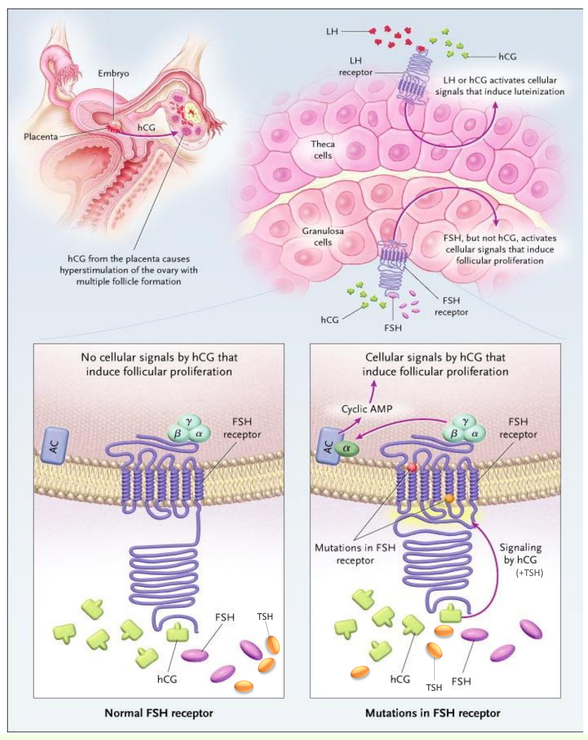

Figure 3. Mutated FSHR can be activated by endogenous hCG triggering sporadic OHSS at the 8th pregnancy week (4).

FSHR mutations and sporadic OHSS

During pregnancy hCG reaches a maximum concentration about 8-10 weeks, which can cross-activate mutated FSHR (*Figure 3*)

Active FSHR stimulates massive follicular recruitment and enlargement.

Granulosa cells of these follicles acquire LH/hCG receptors and finally develop into corpus luteum.

hCG promotes VEGF and VEGFR-2 supraphysiological synthesis and secretion in corpus luteum.

Vascular permeability increases excessively beginning the development of sporadic OHSS.

Clinical approach: Even though FSHR mutations provided, for the first time, an explanation about the aetiology of spontaneous OHSS, as there are sporadic cases in pregnant without any FSHR mutations **the standardized screening of allelic variants in all pregnant women is not currently considered**.

Table 2. FSHR allelic variants and their functional consequences Adapted from OMIM (#608115, *136435)

Authors	Mutation (SNP)	Location in FSHR	Functional consequence of mutated FSHR: Constitutive activity	FSH response	hCG response	TSH response
Vasseur *et al.* (2003)	T449I rs28928870	Exon 10, helix III TMB domain	No	Yes	Yes	No
Smits *et al.* (2003)	D567N rs28928871	Exon 10, helix VI TMB domain	Yes	Yes	Yes	Yes
Montanelli *et al.* (2004)	T449A rs121909663	Exon 10, helix III TMB domain	Yes	Yes	Yes.	Yes
De Leeener *et al.* (2006)	I545T rs121909664	Exon 10, helix V TMB domain	Yes	Yes	Yes	Yes
De Leener *et al.* (2008)	S128Y rs121909665	Exon 5 LRRs in ectodomain	No	Yes	Yes	No

TMB: transmembrane, SNP: single nucleotide polymorphism. Although allelic variants are mainly in transmembrane domain, because of receptor's functional dichotomy between recognition and activation activities, ligand specificity is finally affected.

What about iatrogenic OHSS? →

Nowadays, FSHR polymorphisms have not been related to iatrogenic OHSS. Accordingly, the **preventive screening of these allelic variants in all women before undergoing COS is not also considered**.

In 2000, Al-Hendy defined FSHR gene polymorphisms at two specific sites, **Thr307Ala** and **Ser680Asn,** which reduced FSHR protein responsiveness to exogenous FSH and, as a result, the effectiveness of ovarian stimulation treatment and the likelihood of developing OHSS. Many studies have evaluated the relationship between Ser680Asn and OHSS development (6):

Ser680Asn → Ser680Asn polymorphism is not specific enough to predict the syndrome.
Asn680 is useful to prognosticate the syndrome among OHSS patients → Essential to focus the treatment.

Actual CLINICAL RESEARCH approach

The failure in establishing OHSS aetiology during the last decade has contributed to focus the actual research on the clinical side of the syndrome. The aims of the most recent papers are towards the revision of drugs for the prevention and treatment, and the analysis of long-term consequences.

Dopamine agonists for OHSS prevention/treatment

Dopamine agonists such as **Cabergoline** (Cb2) have been in use since 2002 for OHSS prevention and treatment (*Figure 4*). Recent published meta-analysis conclude that (7):

- Cb2 reduces OHSS incidence among high-risk patients who undergo a COS protocol.
- Results are better if it is used for the prevention than for the treatment.
- Cb2 has no adverse effect on pregnancy as the fertilization and implantation remain unaltered.
- VEGF physiological function is preserved

Although the results, evidences obtained about the benefits of dopamine agonists are still unreliable. Meta-analysis have been judged to be at high risk of selection and information bias, reducing the overall quality.
Nevertheless, the principal limitation of these drugs is that they are only useful for iatrogenic OHSS cases.

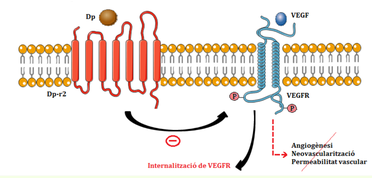

Figure 4. Dopamine action on VEGF/VEFGR-2 pathway. Active Dp-r2 inhibits VEGFR by blocking its intracellular phosphorylation and promoting its internalization.

OHSS and ovarian cancer

A recent study published in 2013 suggested the possible connection between OHSS and a higher risk of ovarian cancer. This speculation was a result of studies which established a relationship between:

- Oestrogen and ovarian cancer
- Ovarian stimulation and ovarian cancer

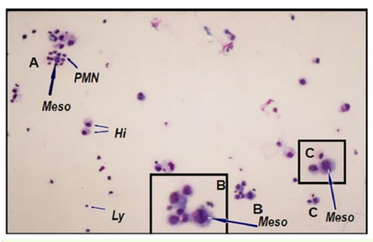

Figure 5. Ascitic fluid with a cytological diagnostic of malignancy. Atypical cells with dark cytoplasm, rough-grained nucleus and multiple nucleoli. (*Ly:leukocytes; Meso:mesothelialcells;Hi:histiocytes;PMN:polymorphonuclear) (B and C 200X)*)

Hatzipetros *et al.* 2013 (8)

Hypothesis: There is a causative relationship between iatrogenic OHSS and ovarian cancer.
Study: Cytology of ascitic fluid cells recovered from patients with severe OHSS and long-term follow-up.
Results: Cytological results suggested ovarian malignancy in most patients (*Figure 5*), but none developed malignant ovarian tumour during the study period.

✖ **No relationship between OHSS and ovarian cancer**
✖ Unreliable results owing to selection bias and ↓n

Clinical research LIMITATION:
All results coming from OHSS clinical research are considered unavoidably of low quality as a consequence of the lack of a standardised definition of high-risk patients, lack of an uniform classification of OHSS severity, lack of standardised protocols used, etc.

CONCLUSIONS

Summarizing the results and discussions of this literature review it can be concluded that:

- Currently OHSS is considered one of the highest risks associated with ART and is described as an idiopathic syndrome because the aetiology has not been completely elucidated.
- Actual research can be divided in a basic and a clinical side, each one with different aims.
- Among high-risk patients there is an individual susceptibility determined by sVEGFR.
- There are genetic cases of OHSS in pregnancy due to FSHR mutations, which broaden its specificity. The detection of carrier pregnant is not contemplated by physicians.
- In sporadic OHSS the allelic variant Asn^{680} is useful as a severity predictor.
- It has been suggested that dopamine agonists reduce OHSS incidence without affecting pregnancy rate and that there is no causative association between OHSS and ovarian cancer.
- It is necessary to standardise the definition, classification and treatment protocols in clinical research.

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